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| EXAMINER | |
|---|---|
| KRISHNAN, GANAPATHY | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/531,853 | DE LUCA ET AL. | |
| | Examiner | Art Unit | |
| | Ganapathy Krishnan | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-48 and 55-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48 and 55-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/05; 12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The Preliminary Amendment of April 18, 2005 presents Claims 1-48 and 55-79 for examination. Claims 49-54 have been cancelled.

### *Specification*

The first page of the WIPO document, WO 2004/035629, filed 04/18/2005, which has an abstract, has also been used as the abstract sheet in the instant specification. This is not acceptable if the instant claims are determined to be allowable at a later stage. The Office requires the abstract to be typed on a separate sheet of paper even though applicants intend using the abstract on the WIPO document for the instant application. Hence, applicants are requested to kindly type the abstract appearing on the first page of the WIPO document (WO 2004/035629) on a separate sheet and file the same.

The disclosure is objected to because of the following informalities:

At page 18, Scheme 6-7, in the reaction depicted at the top, hyaluronic acid is shown to react with a spacer attached to ethylene oxide and the product shown has the spacer attached to the 6-position of the saccharide unit. The methylene groups on the ethylene oxide ring are missing in the structure of the product. Do applicants intend that the term spacer shown attached to the oxygen on the product is inclusive of the two methylene groups from the ethylene oxide? .

At page 30, Scheme 18, depicts the activation of the hydroxyl group of the Taxol followed by attachment to the amino group of the glucosamine moiety. The attachment shown in the product has hydrogen still on the Taxol hydroxyl and also the amine nitrogen is shown as being linked to the Taxol oxygen via a carbonyl group. Is another reagent that introduces a carbonyl group missing?

Appropriate correction is required.

### *Claim Objections*

Claims 32-33 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 32-33 recite limitations as to the order in which the esterification of the hyaluronic acid is performed. These limitations are not seen as further limiting the parent claims since the parent claims are drawn to a product.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-47 and 76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising hyaluronic acid covalently bonded to a taxane and further comprising interferon and the treatment of rheumatoid arthritis, Hashimoto's thyroiditis, systemic lupus erythematosus and glomerulonephritis, does not reasonably provide enablement for a pharmaceutical composition comprising hyaluronic acid covalently bonded to a taxane and further comprising the biologically or pharmaceutically active substances as broadly recited in instant claims 46-47 and the treatment of any auto-immune pathology as broadly encompassed by instant claim 76. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

(A) The breadth of the claims
(B) The state of the prior art
(C)The level of predictability in the art
(D) The amount of direction provided by the inventor
(E) The existence of working examples
(F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

**The breadth of the claims**

Claims 46-47 and 76 are drawn to a pharmaceutical composition comprising hyaluronic acid covalently bonded to a taxane and further comprising the biologically or pharmaceutically active substances and a method of treatment of autoimmune pathologies comprising administering taxane covalently bonded to hyaluronic acid or its derivatives, respectively. The terms, biologically or pharmaceutically active substances are seen merely as a functional language. The terms, biologically or pharmaceutically active substances recited in claim 46 and the broad classes of agents recited in claim 47 and the broad recitation, autoimmune pathologies, recited in claim 76 are also seen to reasonably include not only known compounds and diseases but also unknown compounds and diseases as of the filing date. The breadth of the instant claims is seen to include several compounds, disorders and conditions.

**The state of the prior art**

The examiner notes that the prior art used in the rejection below are drawn to methods of treatment of tumors, cancers and arthritis. However, there is no teaching of the treatment of other diseases and conditions as broadly encompassed by the terms, autoimmune diseases. One of ordinary skill in the art would not extrapolate the information in the prior art to the treatment of all of the diseases and conditions encompassed by the broad recitation, autoimmune pathologies. The art used in the rejection below also teaches only specific antimicrobial and antifungal agents in combination with the Taxol-polymer carrier complexes.

**The level of predictability in the art**

The examiner acknowledges the probability that the instantly claimed compounds may have a reasonable expectation of success. There is not seen sufficient data to substantiate the treatment of all the autoimmune pathologies and the compositions as instantly claimed.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427.2d 833, 166 USPQ (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since on of skill in the art cannot fully visualize or recognize the identity of the members of the genus. In the absence of fully recognizing the identity of the members of the genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having the claimed functional properties in the compositions herein. Goodman and Gilman's "The Pharmacological Basis of Therapeutics", 10$^{th}$ Ed., 1996,

page 54, teaches that the frequency of significant beneficial or adverse drug interactions is unknown (bottom of the left column at page 54). Relatively small changes in the drug level or structure can have significant adverse consequences. In the instant case one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with the many combinations of compounds having the functional properties in the pharmaceutical compositions claimed herein. Thus, the teachings of Gillman and Goodman clearly support that the instantly claimed invention is highly unpredictable.

Autoimmune diseases are characterized by the body's immune responses being directed against its own tissues, causing prolonged inflammation and subsequent tissue destruction. Autoimmune disorders can cause immune-responsive cells to attack the linings of the joints--resulting in rheumatoid arthritis--or trigger immune cells to attack the insulin-producing islet cells of the pancreas leading to insulin-dependent diabetes. A healthy immune system recognizes, identifies, remembers, attacks, and destroys bacteria, viruses, fungi, parasites, and cancer cells or any health-damaging agents not normally present in the body. A defective immune system, on the other hand, wreaks havoc throughout the host by directing antibodies against its own tissues. Any disease in which cytotoxic cells are directed against self-antigens in the body's tissues is considered autoimmune in nature. Such diseases include, but are not limited to, celiac disease, Crohn's disease, pancreatitis, systemic lupus erythematosus, Sjogren's syndrome, Hashimoto's thyroiditis, and other endocrinopathies. Allergies and multiple sclerosis are also the result of disordered immune functioning. It is highly unlikely that the instant composition can treat all autoimmune pathologies that have different etiologies.

**The amount of direction provided by the inventor**

The instant specification is not seen to provide enough guidance that would allow a skilled artisan to extrapolate from the disclosure and the examples provided to enable the treatment of all autoimmune pathologies and compositions comprising taxane covalently bonded to hyaluronic acid and further comprising all of the broad classes of compounds as instantly recited. The specification also fails to direct the skilled artisan in correlative prior art procedures which might provide the basis for the said treatment. The references cited in the instant specification (pages 1-4) are drawn to the use of taxanes and their conjugates for the treatment of cancers.

**The existence of working examples**

The working examples set forth in the instant specification are drawn to the effect of the said compounds/compositions on neoplastic cells in mouse. Despite these examples there is little enabling disclosure for the treatment of all autoimmune diseases. Applicant has given working examples of the effect of the compounds on tumor and cancer cell lines only. Based on this one of ordinary skill in the art cannot predict or extrapolate it to the treatment of all the diseases and conditions as instantly claimed.

**The quantity of experimentation needed to make or use the invention based on the content of the disclosure**

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to enable the compositions and use of the instant compounds/compositions for the treatment of all autoimmune pathologies. One of ordinary skill in the art would have to carry out

experimentation in order to determine the efficacy of the said compounds/compositions in the said methods of treatment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37-38, 55, 58-59, 63, 68, 70, 73 and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 37-38 recite the terms, "bond percentage". Do applicants intend degree of substitution?

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 55 recites the broad recitation medical devices, and the claim also recites stents, which is the narrower statement of the range/limitation. The same recitation is also seen in claim 78.

Claim 58 is drawn to a process for the formation of a thiourethane bond by mixing activated taxane to deacetylated hyaluronic acid. It is not clear how a thiourethane bond can be formed from the said reaction as recited. The same recitation is also seen in claims 63 and 73.

Claim 59 recites the formation of an acetyl bond by adding formaldehyde. An acetyl bond is $CH_3C(O)$-. Reaction with formaldehyde cannot result in the formation of the said bond. Do applicants mean acyl? Regarding claim 59, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). The terms "such as" is also recited in claims 68 and 70. Applicants are also requested to check other claims for the said recitation.

Claim 59 recites the term bounded. It is not clear what applicants intend by this term in this and all other claims in which the said term is recited.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 70 recites the broad recitation

halogen, and the claim also recites bromine, which is the narrower statement of the range/limitation.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-48 and 55-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luo et al (Bioconjugate Chem. 1999, 10, 755-763; document AR cited in IDS of Oct. 03, 2005)

in view of Sparer et al (Controlled Release Delivery Systems, Chapter 6, 1983, 107-119; document AS cited in IDS of Oct. 03, 2005), Li et al (US 5,977,163) and Desai et al (US 5,648,506; document AC cited in the IDS of Oct. 03, 2005).

Luo et al, drawn to bioconjugates, teach conjugates of hyaluronic acid wherein the carboxyl group of the hyaluronic acid is covalently bonded to a linker via an amide linkage to Taxol (Figure 2, page 756). Such conjugates showed selective toxicity towards human cancer cell lines that overexpress hyaluronic acid receptors like CD44 and RHAMM and the conjugates showed no toxicity (page 755, abstract, right column, last paragraph). In addition conjugation of anticancer and antitumor drugs to biopolymers provide advantages in drug stabilization, solubilization, localization and controlled release (page 756, right column, below figure 4). In Figure 2 (page 756), Luo teaches the process for attachment of Taxol to hyaluronic acid wherein the carboxyl of the hyaluronic acid is attached to the spacer via an amide linkage on one end and the other end of the spacer is attached to the hydroxyl of the Taxol via an ester bond. However, the conjugate of Luo comprises hyaluronic acid conjugated to Taxol via a spacer that is a dihydrazide, which is excluded by the proviso in instant claim 1. But one of skill in the art reading Luo's teaching will realize the importance of the conjugate of Taxol and hyaluronic acid since Luo teaches that in addition to advantages with respect to drug stabilization, solubilization and controlled release of the conjugated drug, has the advantage of hyaluronic acid as the carrier, which is immunoneutral and has viscoelastitcity that makes it an excellent joint lubricant, is biocompatible and biodegradable and has been used as a vehicle and angiostatic agent in cancer therapy (page 755, introduction). This means that a conjugate of Taxol, which shows activity

against several cancers and hyaluronic acid, which is biocompatible and has antiinflammtory properties, will have optimal benefits.

Sparer et al, drawn to polysaccharide-drug complexes, teaches glycosaminoglycans including hyaluronic acid are drug carriers because of their favorable properties and have various functional groups available for forming different types of bonds with drugs (page 108, line 1 through page 109, line 3). Sparer reports especially the performance of amide and ester linked glycosaminoglycan drug complexes (page 109, 4-7), which are prepared via standard coupling reaction of the carboxyl group of the hyaluronic acid to the hydroxyl and the amino group of the drug (page 112). According to Sparer's study the release rate from amide complexes was slower and gave a prolonged constant release of the drug. According to Sparer, it would be ideal to obtain zero order release rate in all cases and still be able to vary the rate of release to fit the dosage regimen and this may be possible by selecting a given polymer drug bond and that his studies provide a base from which to design a drug release system. The rate of release may in principle be engineered by the judicious choice of drug-glycosaminoglycan bond based on the hydrolytic stability of the bond (page 117, last paragraph). This means that drug-glycosaminoglycan complexes containing bonds other than amide and ester may be important in controlled release and should be made and studied with respect to their hydrolysis. Even though Sparer does not teach a complex of glycosaminoglycans with Taxol, one of skill in the art will recognize from his teaching that the same could be done using hyaluronic acid and Taxol since both have several functional groups and different types of bonds could be formed between the two molecules with and without a spacer.

However, Luo and Sparer do not teach taxane conjugates, compositions, medical devices coated with the taxane compositions and a method of treating auto immune diseases as instantly claimed.

Li et al, drawn to Taxol complexes, teaches water-soluble complexes of paclitaxel and docetaxel with polyethylene glycol polymers (col. 1, lines 5-14). Their complexes are effective against cancers (col. 5, lines 13-18) and arthritis (col. 5, lines 43-65), and also useful for inhibiting restenosis and coating medical devices like stents (col. 5, line 66 through col. 6, line 43). According to Li such complexes improve the efficacy of anticancer therapy by providing water-soluble and controlled release paclitaxel derived compositions and also eliminate the need for solvents that are associated with side effects (col. 8, lines 34-41). The complexes could be made into compositions comprising excipients and diluents and can be made for different forms of administration. Specific antibacterial and antifungal agents could be added for preservation against microorganisms (col. 10, line 1 through 66). However, Li et al do not teach Taxol hyaluronic acid complexes. But from their teaching one of skill in the art would recognize the use of such complexes in a method of treatment of cancers, tumors, restenosis and coating medical devices.

Desai, drawn to Taxol-carrier conjugates, teaches a process for the attachment of Taxol to carriers via different types of covalent linkages like ester, urethane, amide, amine and ether etc. (col. 4, lines 19-36 and examples 1-5). Even though Desai et al do not exemplify such conjugates using Taxol and hyaluronic acid as instantly claimed, one of skill in the art will recognize that the same type of process steps can be used in the instant process for making Taxol-hyaluronic acid complexes comprising different types of linkages as instantly claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a taxane covalently bonded to hyaluronic acid optionally using a spacer, and use them in a method of treatment and as a coating for medical devices since closely analogous complexes comprising the active agents and their use in treating cancer, restenosis and as coating for medical devices is seen to be taught in the prior art.

One of skill in the art would be motivated to make the complexes as instantly claimed via the process as instantly claimed and use them in a method of treatment as instantly claimed and in coating medical devices since Taxol and hyaluronic acid have many functional groups which makes it possible to make complexes via different type of bonds, which according to Sparer could lead to drug complexes with varied release times, which in turn would extend the duration of treatment. Complexation with hyaluronic acid has the advantage of biocompatibility and also selectivity to cancer cells because of the overexpression of receptors of hyaluronic acid by these cells. The presence of several functional groups in both the agents also helps to make different types of bonds that link both the agents to each other with and without a spacer.

***Conclusion***

Claims 1-48 and 55-79 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GK

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